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Omapatrilat for the Management of Heart Failure and Hypertension

Summary

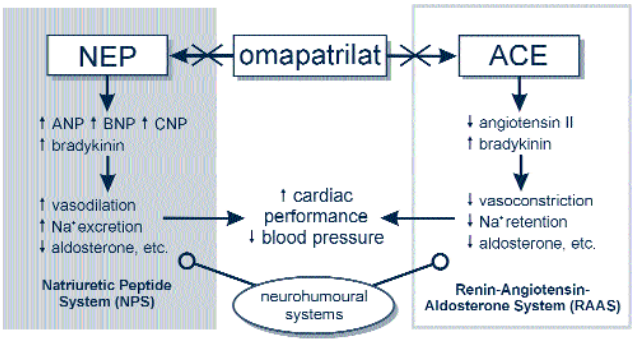
- **Omapatrilat, first in a new class of cardiovascular drugs called vasopeptidase inhibitors, is under evaluation for the management of hypertension and heart failure.**
- **Several small trials have demonstrated the efficacy and tolerability of once-daily omapatrilat in the treatment of mild to moderate hypertension. Efficacy data from one medium-sized trial have demonstrated a benefit comparable to lisinopril in the treatment of systolic heart failure.**
- **The benefits and risks of omapatrilat as compared to ACE inhibitors are under evaluation and could affect future clinical therapy guidelines for managing hypertension and heart failure.**

The Technology

Omapatrilat is the first of a new class of cardiovascular drugs called vasopeptidase inhibitors (VPIs).[1,2] Vasopeptidase inhibition refers to the simultaneous inhibition of angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP; neprilysin). Both enzymes play a key role in fluid balance and the regulation of blood pressure.[2-7] The use of omapatrilat is being investigated for the management of hypertension and heart failure.

Although the benefits of ACE inhibition in the management of cardiovascular disease are well established[8-10] the additional benefits of NEP inhibition are still being explored. These proteins lower blood pressure and improve cardiac output through different biochemical pathways, which can be grouped into neurohumoural systems (see Figure 1).[5,11] The inhibition of NEP alone has been studied in both hypertension and heart failure;[12] however, it has failed to consistently lower blood pressure[5,11] possibly due to a rebound effect - a compensation by another neurohumoural system.[11]

Figure 1: Effects of ACE and NEP Enzyme Inhibition



ANP atrial natriuretic peptide; BNP - brain natriuretic peptide; CNP C-type natriuretic peptide; Na⁺ - sodium; NEP neutral endopeptidase; ACE angiotensin converting enzyme

Regulatory Status

Omapatrilat is being developed by Bristol-Myers Squibb under the trade name Vanlev®. In January 2000, Health Canada granted Bristol-Myers Squibb a priority review for omapatrilat.[13] Omapatrilat was also granted priority review status by the United States Food and Drug Administration (FDA). However, this application was voluntarily withdrawn in April 2000 when the FDA raised concerns about safety.[14,15] As of June 2001, omapatrilat has not been approved for use in Canada.

Patient Group

Omapatrilat is being evaluated for the management of hypertension and heart failure (HF). Hypertension (systolic or diastolic blood pressure $140/90 mm Hg), occurs in 22% of Canadian adults and in 1997 an estimated 1.6 million Canadians were treated for hypertension, which can reduce the risk of cardiovascular events and death.[16-18] Borderline (stage 1) isolated systolic hypertension (ISH, diastolic < 90 mmHg, systolic between 140 and 159 mmHg) becomes increasingly prevalent with age and occurs in nearly one in five men and women by the age of 70.[19]

Heart failure is a complex syndrome characterized by physiological changes that make the heart unable to pump blood adequately. It has been identified as the most common reason for hospital admission in persons aged 65 years and older[5] and accounts for one million

hospitalizations in the U.S. annually.[20] The rate of hospitalization from HF in Canada is greater for men than women and increases with age.[18]

Current Practice

Hypertension is managed through both non-drug therapy (i.e. weight reduction, limited alcohol consumption, sodium restriction, stress reduction, and increased physical activity) and drug therapy.[21,22]

Heart failure, which is caused by left ventricular dysfunction (systolic heart failure), is currently managed by lifestyle modification and the introduction of drug therapy. The use of antihypertensive therapy in the prevention of HF has been well established.[23]

ACE inhibition is a first-line treatment in the management of hypertension and a mainstay in the treatment of HF. ACE inhibition has been shown to reduce mortality and hospitalization in patients with systolic heart failure.[8,10] This appears to be due, in part, to suppression of the overactivated rennin-angiotensin-aldosterone system (Figure 1).[11,24] When compared with conventional therapy (i.e. diuretics, ß-blockers, calcium channel blockers), ACE inhibition shows similar morbidity and mortality outcomes when used to treat hypertension.[9,25,26] These same outcomes are being assessed for VPIs in comparative clinical trials.

Administration and Cost

Pricing and dosage information for omapatrilat is currently unavailable.

Projected Rate of Diffusion

Despite promising early data, concerns about side effects arose when 44 of just under 7000 patients in the U.S. FDA New Drug Application data were reported to have experienced angioedema,[14,27] a rare but potentially life-threatening side-effect. This is higher than the incidence normally associated with ACE inhibitors.[27] As a consequence, Bristol-Myers Squibb voluntarily withdrew their application and is awaiting results from the OCTAVE[a] trial to conclusively assess the safety of omapatrilat.[15,27]

Once an evaluation of safety is concluded, clinically meaningful (i.e. morbidity and mortality) data could have an impact on clinical guidelines for the management of hypertension and HF. If results from two large trials (OVERTURE, OPERA)[b] reveal a benefit with treatment, omapatrilat could be recommended as an alternative to an ACE inhibitor in individuals with HF or borderline ISH. However, morbidity and mortality data for omapatrilat in the initial management of hypertension will be less forthcoming. Decisions to use omapatrilat; however, will not rest entirely on guideline recommendations, which may have only a modest impact on prescribing decisions.[22]

a OCTAVE - Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril

b OVERTURE - Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events
OPERA - Omapatrilat in Persons with enhanced Risk of Atherosclerotic Events

Concurrent Developments

Omapatrilat is the most clinically advanced VPI currently being investigated for hypertension and HF. MDL 100240 (Aventis), sampatrilat (Shire Pharmaceuticals and Roberts Pharmaceutical Corporation), and fasidotril (Bioprojet, France) are being studied in phase II trials.

Assessing The Evidence

Hypertension

Omapatrilat administered orally once daily, in doses above 5 mg significantly ($p < 0.001$) decreases both systolic and diastolic blood pressure.[28] Several placebo-controlled clinical trials have demonstrated the ability of omapatrilat to effectively normalize blood pressure in hypertensives.[29-31] Preliminary studies of omapatrilat in isolated systolic hypertension and individuals unresponsive to thiazides have also shown favourable results. Omapatrilat has also been compared with lisinopril, amlodipine, and losartan[28] but the interpretation of these studies is limited by the lack of reporting proper blinding, randomization or statistics.

Heart Failure

The largest reported, completed randomized controlled trial of omapatrilat to date is the IMPRESS (Inhibition of Metalloprotease by BMS-186716 in a Randomized Exercise and Symptoms Study) trial. The study involved 573 patients in 113 centres who had stable (> 3 months), symptomatic (New York Heart Association Classification Scale II-IV) HF, decreased left-ventricular ejection fraction, and who were receiving a stable (≥4 weeks) dose of an ACE inhibitor. The primary endpoint of the study was a change in exercise duration from baseline to week 12. Patients were randomized to active treatment with 10 mg of omapatrilat titrated to a target dose of 40 mg once daily, or 5 mg lisinopril titrated to a target dose of 20 mg once daily. Patients shared similar baseline and demographic variables. Secondary endpoints for this study included the combined endpoint of death and (hospital) admission for worsening HF, and the combined endpoint of death and comorbidity for worsening HF (admission, discontinuation of study treatment, emergency room visit of clinical need for supplemental diuretic).

No significant difference was seen between omapatrilat and lisinopril for exercise duration. The adjusted mean change from baseline at 12 weeks was 24 seconds (standard error of the mean (SE) = 6 seconds) for the omapatrilat group (n=274) and 31 seconds (SE = 6 seconds) for the lisinopril group (n=265; p=0.45). The combined secondary endpoints of death or admission for worsening HF showed no significant difference (p=0.052) between the omapatrilat (n=14) and lisinopril (n=25) treatment groups. However, the combined secondary endpoint of death and comorbidity occurred less frequently (p=0.035) in the omapatrilat (n=16) group when compared with the lisinopril (n=29) study group.

Currently, omapatrilat is being assessed in three large multicentre trials. The safety and efficacy of omapatrilat is being compared to enalapril in the OCTAVE trial involving a broad range of 25,000 hypertensives.[14,32,33] The trial is expected to conclude mid-2001. OVERTURE is a follow-up trial to the IMPRESS trial. It is a double-blind controlled trial comparing morbidity and mortality from HF in 4420 patients randomized to either enalapril or omapatrilat over a three-year period.[34] OPERA is a double-blind placebo-controlled study designed to look at the effects of omapatrilat in patients with borderline ISH.[35,36] The primary end point of this trial is cardiovascular morbidity and mortality, stroke, heart attack, and heart failure over a follow-up period of 4.25 years.[27]

Implementation Issues

ACE inhibition is a mainstay in the management of all stages of HF. Questions surrounding the role of the natriuretic peptide system in HF and the effects of simultaneous ACE and NEP inhibition should be addressed by ongoing studies. In particular, OVERTURE will measure clinically meaningful outcomes of omapatrilat compared with enalapril, for which benefits have already been demonstrated.

Caution must be exercised; however, when interpreting results from studies in hypertension. Lowering blood pressure alone may or may not result in clinically meaningful outcomes (i.e. reductions in morbidity and mortality). Although preliminary studies have shown statistically significant reductions in blood pressure, clinically meaningful outcomes, such as reduced hospitalization from cardiovascular events or death, are not available. Comparisons with other agents (i.e. low dose thiazides) for which there is convincing evidence of these outcomes, are also absent. Unfortunately, these data usually appear long after a drug is approved for hypertension. Studies of omapatrilat in certain hypertensive disease states (e.g. ISH, diabetes) will be of particular interest.

Omapatrilat is well tolerated and can be used in patients with reduced renal function.[37] However, the overall toxicity and safety of omapatrilat, including the overall incidence of angioedema, is uncertain and must be determined. Results from the OCTAVE trial should indicate the relative safety of these agents when compared with ACE inhibitors. Ultimately, any increased risk observed with this new drug will need to be justified by an observed greater impact on morbidity and mortality in multiple comparative trials. This balance between benefit and risk will eventually determine the place of omapatrilat in the management of cardiovascular disease.

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